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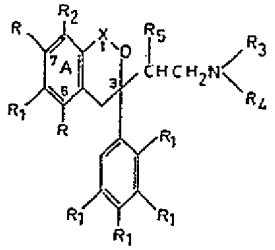
(54) AMINOALKYL-ISOCHROMANS AND ISOCOUMARINS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4000 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel tertiary aminoethyl isochromans and isocoumarins.

The invention provides compounds of formula I,



I

in which each

R independently signifies hydrogen, trifluoromethyl or alkyl or alkoxy of 1 to 5 carbon atoms, each

R_1 independently signifies hydrogen, fluorine, chlorine, trifluoromethyl or alkyl or alkoxy of 1 to 5 carbon atoms, or two R_1's on adjacent carbon atoms together signify methylenedioxy,

R_2 signifies hydrogen, trifluoromethyl, alkoxy of 1 to 5 carbon atoms, fluorine or chlorine,

R_3 and R_4 independently signify alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms or benzyl, or

R_3 and R_4 together signify a $—(CH_2)—$ chain of 4 to 7 carbon atoms or

$$—(CH_2)_2—Z—(CH_2)_2—$$

in which Z signifies oxygen or sulphur or nitrogen substituted by alkyl of 1 to 5 carbon atoms,

R_5 signifies hydrogen or straight chain alkyl of 1 to 5 carbon atoms and

X signifies $—CH_2—$ or $—CO—$, with the provisos that

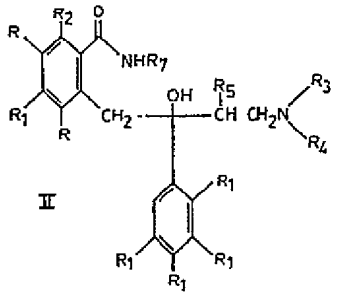
i) no more than three of R, R_1 and R_2 are other than hydrogen and no more than two of R, R_1 and R_2 are other than hydrogen on any one ring, and

ii) R_1 and R_2 on ring A are not both halo, and

iii) no two trifluoromethyl groups are on adjacent carbon atoms.

The invention also provides processes for the production of compounds of formula I, which comprise

a) cyclising by heating to at least 100°C a compound of formula II,



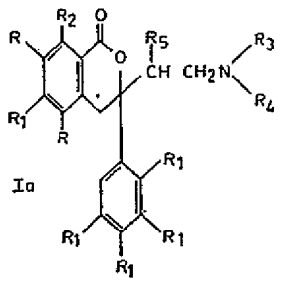
II

in which

R, R_1, R_2, R_3, R_4 and R_5 and the provisos are as defined above, and

R_7 signifies alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms or benzyl, to form a compound of formula Ia,

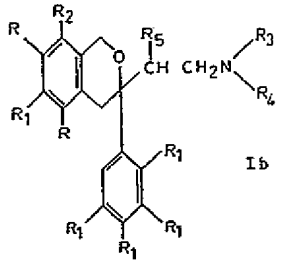
[*Price 25p*]



Ia

in which
R, R_1, R_2, R_3, R_4 and R_5 and the provisos are as defined above, or

b) reducing using an alkali metal borohydride, in an inert organic solvent and at a temperature of −20 to 80°C and in the presence of borontrifluoride etherate a compound of formula Ia as defined above, and treating the resulting adduct with concentrated acid at a temperature of from 40°C to the reflux temperature of the reaction mixture, to form a compound of formula Ib,



Ib

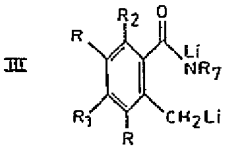
in which
R, R_1, R_2, R_3, R_4 and R_5 and the provisos are as defined above.

Process variant a) is preferably carried out in an inert organic solvent such as an ether, e.g. ethyl ether, or a hydrocarbon or halogenated hydrocarbon, e.g. hexane, heptane, benzene, toluene or *o* - dichlorobenzene. The preferred reaction temperature is from 140 to 160°C. Although temperatures as high as 220 or 250°C may be used. Reaction times are usually about 15 to 48 hours, under preferred conditions about 20 to 28 hours. Carrying the reaction out in the absence of oxygen, for example under inert atmosphere, such as under nitrogen, tends to increase yields and give a better quality product.

In process variant b) the compound of formula Ia may be in free base or acid addition salt form. The reducing agent is preferably sodium or lithium borohydride. The inert organic solvent is suitably tetrahydrofuran or diethyleneglycoldimethylether (diglyme). The reaction is preferably carried out at elevated temperature, especially from 50 to 60°C, and the reaction may be effected for about 1/2 to 2 hours, and under preferred conditions about 1 hour. The particular solvent or temperature used is not critical. In the treatment of the adduct with concentrated acid, the acid is suitably concentrated hydrochloric or sulphuric acid, or, preferably, glacial acetic acid. The reaction may be carried out in an inert organic solvent such as ether or tetrahydrofuran, and is preferably carried out at the reflux temperature of the reaction mixture. Neither the temperature nor the solvents used are critical. In this process, it is convenient to remove the solvent used in the first step, without isolation of the intermediate, and introduce suitable solvent for the second step.

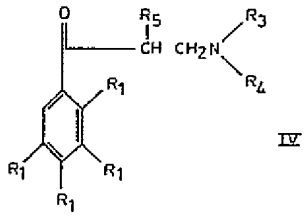
The compounds of formula Ia and Ib may be recovered and purified using conventional techniques such as crystallization.

The compounds of formula II may be prepared by condensing a compound of formula III,



III

in which
R, R_1, R_2 and R_7 are as defined above, with a compound of formula IV,



IV

in which
R_1, R_3, R_4 and R_5 are as defined above, in an inert organic solvent and in the absence of oxygen, and hydrolyzing the reaction product.

The inert solvent is suitably diethyl ether, tetrahydrofuran, hexane, heptane or benzene, and the reaction is conveniently carried out under an inert gas, e.g. nitrogen. Suitable reaction temperatures are from −80 to −20°C, preferably −60 to −40°C, and it is preferred to add the compound of formula IV in inert solvent to a cold (−60 to −40°C) inert solvent solution of the compound of formula III. Reaction times are about 1 to 3 hours. The hydrolysis is effected in conventional manner, preferably with aqueous ammonium chloride and preferably at a temperature of about −20 to 0°C. The solvents, temperatures and hydrolysing agents used are not critical. The compounds of

formula II may be recovered and purified using conventional techniques.

Certain of the compounds of formulae III and IV are known and may be prepared by methods disclosed in the literature. Those compounds not specifically disclosed may be prepared by analogous methods from known materials.

It will be understood that certain of the compounds of formulae I and II exist in racemic form, or in the form of optically active isomers. Additionally, some of the compounds of formula I, particularly those in which R_5 signifies alkyl, may also exist as diastereomeric isomers. The separation and recovery of the isomers may be accomplished using conventional techniques and such isomers are included within the scope of this invention.

The compounds of formula I possess pharmacological activity. More particularly, they possess diuretic activity as indicated, e.g., by their activity in the unanesthetized rat when tested basically as described by R. Aston, Toxical. and Appl. Pharmacol. *1*, 277 (1959).

The compounds also possess hypotensive/antihypertensive activity as indicated, e.g., by their activity in hypertensive rat when tested basically as described by A. Grollman (Proc. Soc. Exptl. Biol. and Med. *57*; 103 (1944).

The compounds are therefore indicated for use as hypotensive/antihypertensives or diuretics. The indicated daily dosage for both indicated uses is in the range from 50 to 1500 mg, conveniently administered in divided or unit doses containing from 12.5 to 750 mg of active compound, 2 to 4 times a day, or in sustained release form.

A particularly interesting compound is 3 - [2 - (dimethylamino)ethyl] - 3 - phenyl isochroman.

For the above indicated uses, the compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such salt forms possess the same order of activity as the free base, and are readily prepared by reacting the free base with an appropriate acid and accordingly are included within the scope of the invention. Suitable such salt forms include mineral acid salts such as the hydrochloride, hydrobromide, sulphate and phosphate and organic acid salts such as the succinate, benzoate, acetate, *p* - toluenesulphonate and benzenesulphonate. Acid addition salt forms may be converted into free base form by conventional methods such as treatment of an aqueous solution with a base such as sodium hydroxide.

The invention also provides a pharmaceutical composition comprising a compound of formula I, in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutically acceptable carrier or diluent.

A representative formulation suitable for oral administration is a capsule prepared by standard techniques which contains the following:

Ingredient	Parts by Weight
Compound of formula I, e.g. 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin	25
Inert filler (starch, kaolin, lactose etc.)	275

The following Examples 2 and 3 illustrate the invention. Example 1 illustrates the production of intermediates.

EXAMPLE 1

o - {α - [2 - (dimethylamino)ethyl] - α - hydroxy)phenethyl - N - methyl benzamide (compound of formula II)

To a flask equipped with a stirrer, dropping funnel, condenser and gas inlet tube and maintained under a nitrogen atmosphere there is added at room temperature 40.0 g (0.28 mole) of *o* - methyl - N - methyl benzamide and 250 ml of anhydrous tetrahydrofuran. The reaction flask is immersed in an ice bath and cooled to an internal temperature of 5°C. Stirring is initiated and 380 ml of 1.6 molar n - butyllithium (0.616 mole) in hexane is added dropwise in *ca.* 1 hour, maintaining the temperature below 8°C. The resulting red dilithio salt is stirred at 5°C for 1 additional hour and the reaction flask is then immersed in a dry-ice/acetone bath and cooled to an internal temperature of —60°C. To the cold reaction mixture a solution of 49.7 g (0.28 mole) 3 - dimethylaminopropiophenone in 140 ml anhydrous tetrahydrofuran is added dropwise in *ca.* 45 minutes maintaining the temperature between —60 and —50°C. The resulting reaction mixture is stirred at —60°C for 1 hour, allowed to warm to 0°C in *ca.* 1 hour, and then treated with 200 ml of saturated aqueous ammonium chloride while maintaining the temperature below 10°C. The resulting solid is filtered, washed thoroughly with water and recrystallised from methylene chloride/ether (1:1) to give o - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - methyl benzamide; m.p. 139.5—140.5°C.

When the above process is carried out and

a) o - methyl - N - allyl benzamide, or

b) o - methyl - N - benzyl benzamide is used in place of o - methyl - N - methyl benzamide, there is obtained

a) o - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - allyl benzamide, or

b) o - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - benzyl benzamide, respectively.

When the above detailed process is carried out and in place of o - methyl - N - methyl benzamide there is used

c) 2 - methyl - 6 - methoxy - N - methyl benzamide,

d) 4 - chloro - 2 - methyl - N - methyl benzamide,

e) 2,3 - dimethyl - N - methyl benzamide, or

f) 2 - methyl - 5 - trifluoromethyl - N - methyl benzamide, there is obtained

c) 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - 6 - methoxy - N - methyl benzamide,

d) 4 - chloro - 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - methyl benzamide,

e) 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - 3,N - dimethyl benzamide, or

f) 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - 5 - trifluoromethyl - N - methyl benzamide, respectively.

When the above detailed procedure is carried out and in place of 3 - dimethylaminopropiophenone there is used

g) 3',4' - dichloro - 3 - dimethylaminopropiophenone,

h) 3 - dimethylamino - 4' - methoxypropiophenone,

i) 3 - (N - methylpiperazino)propiophenone,

j) 3 - morpholinopropiophenone,

k) 3 - dimethylamino - 2 - methylpropiophenone,

l) 3 - thiomorpholinopropiophenone,

m) 3 - pyrrolidylpropiophenone,

n) 3 - piperidinylpropiophenone,

o) 3 - diallylamino - 2' - methylpropiophenone,

p) 3 - dibenzylamino - 3' - trifluoromethylpropiophenone, or

q) 3 - dimethylamino - 3',4' - methylenedioxypropiophenone, there is obtained

g) o - {3,4 - dichloro - α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - methyl benzamide, m.p. 130—131°C,

h) *o* - {α - [2 - (dimethylamino)ethyl] - α - hydroxy - *p* - methoxy}phenethyl - N - methyl benzamide,

i) o - {α - hydroxy - α - [2 - (N - methylpiperazino)ethyl]}phenethyl - N - methyl benzamide,

j) o - {α - hydroxy - α - [2 - (morpholino)ethyl]}phenethyl - N - methyl benzamide,

k) o - {α - (2 - dimethylamino - 1 - methyl)ethyl] - α - hydroxy}phenethyl - N - methyl benzamide,

l) o - {α - hydroxy - α - [2 - (thiomorpholino)ethyl]}phenethyl - N - methyl benzamide,

m) o - {α - hydroxy - α - [2 - (pyrrolidyl)ethyl]}phenethyl - N - methyl benzamide,

n) o - {α - hydroxy - α - [2 - (piperidinyl)ethyl]}phenethyl - N - methyl benzamide,

o) o - {α - [2 - (diallylamino)ethyl] - α - hydroxy - o - methyl}phenethyl - N - methyl benzamide,

p) o - {α - [2 - (dibenzylamino)ethyl] - α - hydroxy - m - trifluoromethyl}phenethyl - N - methyl benzamide, or

q) o - {α - [2 - (dimethylamino)ethyl] - α - hydroxy - 3,4 - methylenedioxy}phenethyl - N - methyl benzamide, respectively.

EXAMPLE 2

3 - [2 - (Dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin [process variant a)]

To a flask equipped with a stirrer, condenser and gas inlet tube and maintained under a nitrogen atmosphere there is added at room temperature 16.3 g (0.05 mole) of o - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - methyl benzamide and 170 ml of *o* - dichloro benzene. Stirring is initiated and the mixture is heated at reflux for 18 hours. The excess *o* - dichlorobenzene is then removed by distillation in vacuo and the resulting oil is crystallized from ether to give 3 - [2 - (dimethylamino)-ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin; m.p. 95.0—95.5°C.

When the above process is carried out and in place of o - {α - [2 - (dimethylamino)-ethyl] - α - hydroxy}phenethyl - N - methyl benzamide there is used

a) *o* - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - allyl benzamide,

b) *o* - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - benzyl benzamide,

c) 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - 6 - methoxy - N - methylbenzamide,

d) 4 - chloro - 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - methylbenzamide,

e) 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - 3,N - dimethyl benzamide,

f) 2 - {α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - 5 - trifluoromethyl - N - methyl benzamide,

g) *o* - {3,4 - dichloro - α - [2 - (dimethylamino)ethyl] - α - hydroxy}phenethyl - N - methyl benzamide,

h) *o* - {α - [2 - (dimethylamino)ethyl] - α - hydroxy - *p* - methoxy}phenethyl - N - methyl benzamide,

i) *o* - {α - hydroxy - α - [2 - (N - methylpiperazino)ethyl]}phenethyl - N - methyl benzamide,

j) *o* - {α - hydroxy - α - [2 - (morpholino)-ethyl]}phenethyl - N - methyl benzamide,

k) *o* - {α - [2 - (dimethylamino - 1 - methylethyl] - α - hydroxy}phenethyl - N - methyl benzamide,

l) *o* - {α - hydroxy - α - [2 - thiomorpholino)ethyl]}phenethyl - N - methyl benzamide,

m) *o* - {α - hydroxy - α - [2 - (pyrrolidyl)-ethyl]}phenethyl - N - methyl benzamide,

n) *o* - {α - hydroxy - α - [2 - (piperidinyl)-ethyl]}phenethyl - N - methyl benzamide,

o) *o* - {α - [2 - (diallylamino)ethyl] - α - hydroxy - *o* - methyl}phenethyl - N - methyl-benzamide,

p) *o* - {α - [2 - (dibenzylamino)ethyl] - α - hydroxy - *m* - trifluoromethyl}phenethyl - N - methyl benzamide, or

q) *o* - {α - [2 - (dimethylamino)ethyl] - α - hydroxy - 3,4 - methylenedioxy}phenethyl N - methyl benzamide, there is obtained

a) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin, m.p. 95.0—95.5°C,

b) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin, m.p. 95.0—95.5°C,

c) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 8 - methoxy - 3 - phenyl isocoumarin,

d) 6 - chloro - 3 - [2 - (dimethylamino)-ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin,

e) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 5 - methyl - 3 - phenyl isocoumarin,

f) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl - 7 - trifluoromethyl isocoumarin,

g) 3 - (3,4 - dichlorophenyl) - 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro isocoumarin, m.p. in hydrochloride salt form, 286—287°C,

h) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - (*p* - methoxyphenyl) isocoumarin, m.p. 87—88°C,

i) 3,4 - dihydro - 3 - [2 - (N - methyl-piperazino)ethyl] - 3 - phenyl isocoumarin, m.p. 134—135.5°C,

j) 3,4 - dihydro - 3 - [2 - (morpholino)-ethyl] - 3 - phenyl isocoumarin, m.p. 120—121°C,

k) 3 - {[2 - (dimethylamino) - 1 - methyl]-ethyl} - 3,4 - dihydro - 3 - phenyl isocoumarin, m.p. 132—134°C,

l) 3,4 - dihydro - 3 - phenyl - 3 - [2 - (thiomorpholino)ethyl]isocoumarin,

m) 3,4 - dihydro - 3 - phenyl - 3 - [2 - (pyrrolidyl)ethyl]isocoumarin,

n) 3,4 - dihydro - 3 - phenyl - 3 - [2 - (piperidinyl)ethyl]isocoumarin,

o) 3 - [2 - (diallylamino)ethyl] - 3,4 - dihydro - 3 - (*o* - methylphenyl)isocoumarin, m.p. 173.5—174.5°C,

p) 3 - [2 - (dibenzylamino)ethyl] - 3,4 - dihydro - 3 - (*m* - trifluoromethylphenyl)-isocoumarin, or

q) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - (3,4 - methylenedioxyphenyl)-isocoumarin, respectively.

EXAMPLE 3

3 - [2 - (Dimethylamino)ethyl] - 3 - phenyl isochroman (process variant b))

To a solution of 13.0 g (0.042 mole) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin in 220 ml diglyme was added in one portion 177 g (160 ml) (0.126 mole) of boron trifluoride etherate. The resulting mixture was added dropwise with stirring to a solution of 3.2 g sodium borohydride (0.084 mole) in 220 ml diglyme, maintaining the temperature at 0°C. After the addition was complete the resulting mixture was heated at 55°C for 1 hour and then cooled in ice and treated dropwise with 100 ml water, maintaining the temperature at about 5°C. The solvents were removed *in vacuo* and the residue treated with ether. The insoluble boronhydride adduct was dissolved in 320 ml tetrahydrofuran containing 120 ml glacial acetic acid and refluxed for 4 hours. The solvents were removed *in vacuo* and the residue dissolved in water and made basic by the addition of solid potassium hydroxide and extracted with ether. The ether was dried over anhydrous magnesium sulfate and filtered, cooled in ice and treated with gaseous hydrogen chloride and the resulting solid was filtered and recrystallized from methylene chloride/ether to give the product 3 - [2 - (dimethylamino)ethyl] - 3 - phenyl isochroman hydrochloride, m.p. 164.5—165.0°C.

When the above process is carried out and in place of 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin there is used

a) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 8 - methoxy - 3 - phenyl isocoumarin,

b) 6 - chloro - 3 - [2 - (dimethylamino)-ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin,

c) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 5 - methyl - 3 - phenyl isocoumarin,

d) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl - 7 - trifluoromethyl isocoumarin,

e) 3 - (3,4 - dichlorophenyl) - 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro isocoumarin,

f) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - (*p* - methoxyphenyl)isocoumarin,

g) 3,4 - dihydro - 3 - (2 - (N - methyl-piperazino)ethyl] - 3 - phenyl isocoumarin,

h) 3,4 - dihydro - 3 - [2 - (morpholino) - ethyl] - 3 - phenyl isocoumarin,

i) 3 - {[2 - (dimethylamino) - 1 - methyl]-ethyl} - 3,4 - dihydro - 3 - phenyl isocoumarin,

j) 3,4 - dihydro - 3 - phenyl - 3 - [2 - (thiomorpholino)ethyl]isocoumarin,

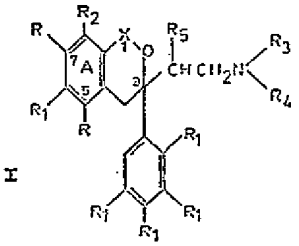
k) 3,4 - dihydro - 3 - phenyl - 3 - [2 - (pyrrolidyl)ethyl]isocoumarin,

l) 3,4 - dihydro - 3 - phenyl - 3 - [2 - (piperidinyl)ethyl]isocoumarin,

m) 3 - [2 - (diallylamino)ethyl] - 3,4 - dihydro - 3 - (*o* - methylphenyl)isocoumarin,
n) 3 - [2 - (dibenzylamino)ethyl] - 3,4 - dihydro - 3 - (*m* - trifluoromethylphenyl)-isocoumarin, or
o) 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - (3,4 - methylenedioxyphenyl)-isocoumarin, respectively there is obtained as the hydrochloride
a) 3 - [2 - (dimethylamino)ethyl] - 8 - methoxy - 3 - phenyl isochroman,
b) 6 - chloro - 3 - [2 - (dimethylamino)-ethyl] - 3 - phenyl isochroman,
c) 3 - [2 - (dimethylamino)ethyl] - 5 - methyl - 3 - phenyl isochroman,
d) 3 - [2 - (dimethylamino)ethyl] - 3 - phenyl - 7 - trifluoromethyl isochroman,
e) 3 - (3,4 - dichlorophenyl) - 3 - [2 - (dimethylamino)ethyl] isochroman,
f) 3 - [2 - (dimethylamino)ethyl - 3 - (*p* - methoxyphenyl)isochroman, m.p. in succinate salt form 136.5—137.5°C,
g) 3 - [2 - (N - methylpiperazino)ethyl] - 3 - phenyl isochroman,
h) 3 - [2 - (morpholino)ethyl] - 3 - phenyl isochroman,
i) 3 - {[2 - (dimethylamino) - 1 - methyl]-ethyl} - 3 - phenyl isochroman,
j 3 - phenyl - 3 - [2 - (thiomorpholino)-ethyl]isochroman,
k) 3 - phenyl - 3 - [2 - (pyrrolidyl)ethyl]-isochroman,
l) 3 - phenyl - 3 - [2 - (piperidinyl)ethyl]-isochroman,
m) 3 - [2 - (diallylamino)ethyl] - 3 - (*o* - methylphenyl)isochroman,
n) 3 - [2 - (dibenzylamino)ethyl] - 3 - (*m* - trifluoromethylphenyl)isochroman, or
o) 3 - [2 - (dimethylamino)ethyl] - 3 - (3,4 - methylenedioxyphenyl)isochroman, respectively.

WHAT WE CLAIM IS:—

1. Processes for the production of compounds of formula I,



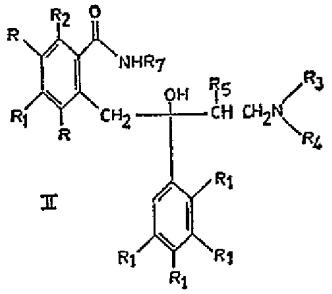
I

in which each
R independently signifies hydrogen, trifluoromethyl or alkyl or alkoxy of 1 to 5 carbon atoms, each
R_1 independently signifies hydrogen, fluorine, chlorine, trifluoromethyl or alkyl or alkoxy of 1 to 5 carbon atoms, or two R_1's on adjacent carbon atoms together signify methylenedioxy,
R_2 signifies hydrogen, trifluoromethyl, alkoxy of 1 to 5 carbon atoms, fluorine or chlorine,
R_3 and R_4 independently signify alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms or benzyl, or
R_3 and R_4 together signify a $—(CH_2)—$ chain of 4 to 7 carbon atoms or

$$—(CH_2)_2—Z—(CH_2)_2—$$

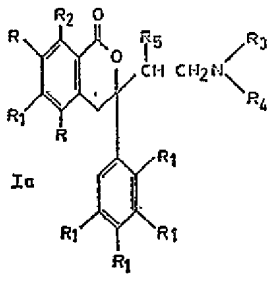
in which Z signifies oxygen or sulphur or nitrogen substituted by alkyl of 1 to 5 carbon atoms,
R_5 signifies hydrogen or straight chain alkyl of 1 to 5 carbon atoms and
X signifies $—CH_2—$ or —CO—, with the provisos that
i) no more than three of R, R_1 and R_2 are other than hydrogen and no more than two of R, R_1 and R_2 are other than hydrogen on any one ring, and
ii) R_1 and R_2 on ring A are not both halo, and
iii) no two trifluoromethyl groups are on adjacent carbon atoms, which comprise

a) cyclising by heating to at least 100°C a compound of formula II,



II

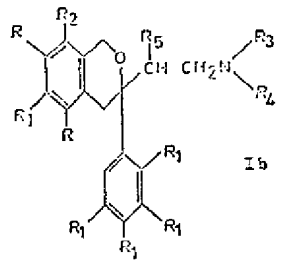
in which
R, R_1, R_2, R_3, R_4 and R_5 and the provisos are as defined above, and
R_7 signifies alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms or benzyl, to form a compound of formula Ia,



Ia

in which
R, R_1, R_2, R_3, R_4 and R_5 and the provisos are as defined above, or

b) reducing using an alkali metal borohydride, in an inert organic solvent and at a temperature of −20 to 80°C and in the presence of borontrifluoride etherate a compound of formula Ia as defined above, and treating the resulting adduct with concentrated acid at a temperature of from 40°C to the reflux temperature of the reaction mixture, to form a compound of formula Ib,



Ib

in which

R_1, R, R_2, R_3, R_4 and R_5 and the provisos are as defined above.

2. A process according to claim 1, in which the compound of formula II is heated to a temperature of from 140° to 160°C, in an inert organic solvent and under an inert atmosphere.

3. A process according to claim 1, in which the compound of formula Ia is reduced with sodium or lithium borohydride and the resulting adduct is treated with concentrated hydrochloric or sulphuric acid or with glacial acetic acid.

4. A process according to Claim 1, 2 or 3, in which a resulting free base form of the compound of formula I is converted into an acid addition salt form, or *vice versa*.

5. A process according to Claim 1, substantially as hereinbefore described with reference to Example 2 or 3.

6. A compound of formula I, whenever prepared by a process according to any one of Claims 1 to 5.

7. A compound of formula I, as defined in Claim 1.

8. 3 - [2 - (Dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin.

9. 3 - (3,4 - Dichlorophenyl) - 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro isocoumarin.

10. 3 - [2 - (Dimethylamino)ethyl] - 3,4 - dihydro - 3 - (*p* - methoxyphenyl)isocoumarin.

11. 3,4 - Dihydro - 3 - [2 - (N - methylpiperazino)ethyl] - 3 - phenyl isoccumarin.

12. 3,4 - Dihydro - 3 - [2 - (morpholino)ethyl] - 3 - phenyl isocoumarin.

13. 3 - {[2 - (Dimethylamino) - 1 - methyl]ethyl} - 3,4 - dihydro - 3 - phenyl isocoumarin.

14. 3 - [2 - (Dimethylamino)ethyl] - 3 - phenyl isochroman.

15. 3 - [2 - (Dimethylamino)ethyl] - 3 - (*p* - methoxyphenyl)isochroman.

16. 3 - [2 - (Dimethylamino)ethyl] - 3,4 - dihydro - 8 - methoxy - 3 - phenyl isocoumarin.

17. 6 - Chloro - 3 - [2 - (dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl isocoumarin.

18. 3 - [2 - (Dimethylamino)ethyl] - 3,4 - dihydro - 5 - methyl - 3 - phenyl isocoumarin.

19. 3 - [2 - (Dimethylamino)ethyl] - 3,4 - dihydro - 3 - phenyl - 7 - trifluoromethyl isocoumarin.

20. 3,4 - Dihydro - 3 - phenyl - 3 - [2 - (thiomorpholino)ethyl]isocoumarin.

21. 3,4 - Dihydro - 3 - phenyl - 3 - [2 - (pyrrolidyl)ethyl]isocoumarin.

22. 3,4 - Dihydro - 3 - phenyl - 3 - [2 - (piperidyl)ethyl]isocoumarin.

23. 3 - [2 - (Dibenzylamino)ethyl] - 3,4 - dihydro - 3 - (*m* - trifluoromethylphenyl)-isocoumarin.

24. 3 - [2 - (Dimethylamino)ethyl] - 3,4 - dihydro - 3 - (3,4 - methylenedioxyphenyl)-isocoumarin.

25. 3 - [2 - (Dimethylamino)ethyl] - 8 - methoxy - 3 - phenyl isochroman.

26. 6 - Chloro - 3 - [2 - (dimethylamino)-ethyl] - 3 - phenyl isochroman.

27. 3 - [2 - (Dimethylamino)ethyl] - 5 - methyl - 3 - phenyl isochroman.

28. 3 - [2 - (Dimethylamino)ethyl] - 3 - phenyl - 7 - trifluoromethyl isochroman.

29. 3 - (3,4 - Dichlorophenyl) - 3 - [2 - (dimethylamino)ethyl]isochroman.

30. 3 - [2 - (N - methylpiperazino)ethyl] - 3 - phenyl isochroman.

31. 3 - [2 - (Morpholino)ethyl] - 3 - phenyl isochroman.

32. 3 - {[2 - (dimethylamino - 1 - methyl]-ethyl} - 3 - phenyl isochroman.

33. 3 - Phenyl - 3 - [2 - (thiomorpholino)-ethyl]isochroman.

34. 3 - Phenyl - 3 - [2 - (pyrrolidyl)ethyl]-isochroman.

35. 3 - Phenyl - 3 - [2 - (piperidinyl)-ethyl]isochroman.

36. 3 - [2 - (Diallylamino)ethyl] - 3 - (*o* - methylphenyl)isochroman.

37. 3 - [2 - (Dibenzylamino)ethyl] - 3 - (*m* - trifluoromethylphenyl)isochroman.

38. 3 - [2 - (Dimethylamino)ethyl] - 3 - (3,4 - methylenedioxyphenyl)isochroman.

39. 3 - [2 - (Diallylamino)ethyl] - 3,4 - dihydro - 3 - (*o* - methylphenyl)isocoumarin.

40. A compound according to any one of Claims 6 to 39, in acid addition salt form.

41. A pharmaceutical composition comprising a compound according to any one of Claims 6 to 39, in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutically acceptable carrier or diluent.

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